Chemical Science

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DOI: 10.1039/D5SC05582B

EDGE ARTICLE

Construction of α-Quinonyl-α-Hydroxy/Amino Acid Esters through Redox Chain Reaction

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Received 00th January 20xx,
Accepted 00th January 20xx

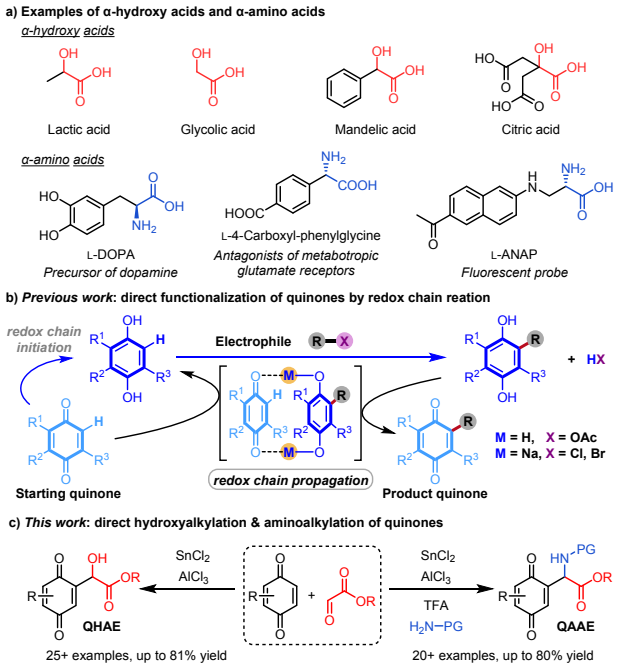
DOI: 10.1039/x0xx00000x

Despite quinones, α-hydroxy acids and α-amino acids are all widely used organic compounds in numerous fields, compounds based on the combination of these motifs were underexplored. In this study, the direct hydroxyalkylation of quinones with glyoxylates was developed through a redox chain reaction using $SnCl_2$ as the reductive initiator and catalyst, and $AlCl_3$ as the co-catalyst. Various α-quinonyl-α-hydroxyacetyl esters were obtained under mild conditions in up to 81% yield within a few hours. Substrates with different ester groups were accessed through *in situ* oxidation of corresponding tartrates to glyoxylates by PIDA. Moreover, aminoalkylation of quinones was achieved by multicomponent reaction of quinones, glyoxylates and amides, affording a series of α-quinonyl-α-aminoacetyl esters in up to 80% yield. The products were easily converted to unnatural amino acids, aryl azo compounds and peptides as demonstrations of their wide potential applications.

Introduction

α-Hydroxy[1-4] and α-amino[5-9] acids are widespread motifs in biological and pharmaceutical molecules (Scheme 1a). Artificially synthesized unnatural amino acids potentially provide distinctive functions beyond existing natural amino acids for biology and chemistry.[10, 11] Despite significant research progress in this field, reports on quinone-substituted amino acid derivatives are limited.[12-14] Based on their redox properties, quinones could serve as mediators for cellular electron transfer processes.[15-20] The quinones are also very versatile platform for further functionalization and conjugation with other molecules. Introducing quinones into the side chain of amino acids may enable new functional unnatural amino acids and related materials. In recent years, structural modifications of quinones have significantly advanced.[17, 21-24] Among all the existing protocols, our group made the original contributions of a unique and efficient strategy for direct quinone functionalization with various sp^3 electrophiles, the redox chain reaction (Scheme 1b).[25-28] With this new strategy, quinones can be functionalized in one step, bypassing the traditional reduction-functionalization-oxidation sequence. Herein, we report that many densely functionalized α-quinonyl-α-hydroxy and amino acetyl esters (QHAE and QAAE) are constructed by redox chain reaction of quinones with glyoxylates[29, 30] and their imines as uncharted sp^2 electrophiles, using $SnCl_2$ as both the reductive initiator and the main Lewis acid catalyst, along with $AlCl_3$ as a Lewis acid co-catalyst (Scheme 1c).[31]

Scheme 1. α-hydroxy and amino acid motifs



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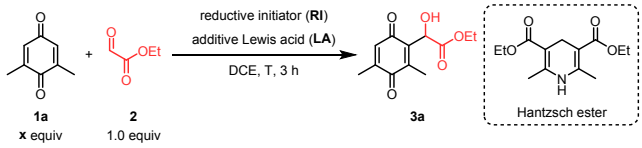
† Electronic supplementary information (ESI) available: Experimental details and supplemental tables. CCDC 2427751. For ESI and crystallographic data in CIF, see DOI: 10.1039/x0xx00000x

Results and discussion

To investigate the conditions, 2,6-dimethylquinone **1a** and ethyl glyoxylate **2** were chosen as the model substrates. Initial investigation used Hantzsch ester (HE) as the reductive initiator, and different Lewis acids were surveyed at 30 °C in 1,2-dichloroethane (DCE) (Table 1, Entries 1-6). The combination of HE and $Hf(OTf)_4$ could not provide higher than 63% QHAE product **3a**, likely because of the basicity of the HE oxidation product. Reductive Lewis acids were then considered to replace both HE and $Hf(OTf)_4$ (Table 1, Entries 7-10). Using 5 mol % $SnCl_2$, the reaction afforded 78 % yield of **3a**, which was not improved when doubling the amount of $SnCl_2$. Extra Lewis acids were attempted to improve the reaction efficiency (Table 1, Entries 11-14), and up to 97 % NMR yield was achieved in the presence of 5 mol % of $AlCl_3$. Reducing the amount of quinone **1a** decreased the yield, while further increasing **1a** only marginally improved the yield (Table 1, Entries 15 and 16). When the temperature was lowered to 0°C, the efficiency significantly decreased, whereas raising the temperature to 60°C maintained an 85% yield (Table 1, Entries 17 and 18).

Table 1. Optimization of the reaction conditions[a]

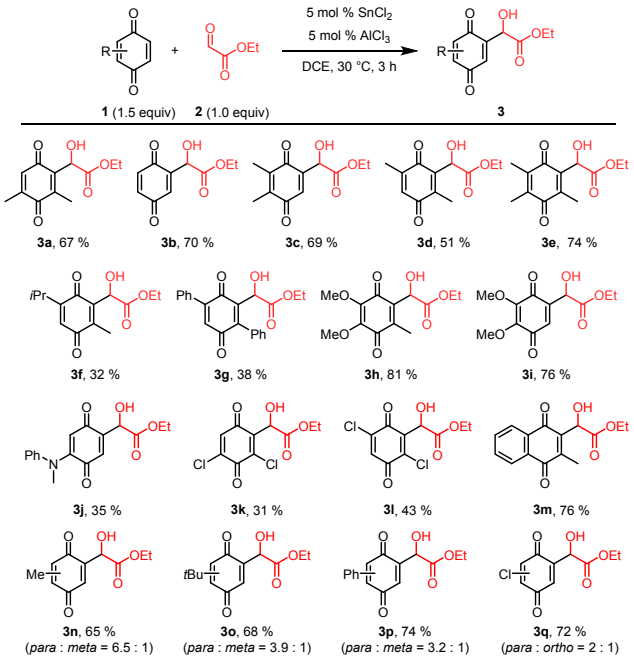


Entry	x	RI / (mol %)	T / °C	LA / (mol %)	yield (%)
1	1.5	HE (10)	30	$Hf(OTf)_4$ (5)	63
2	1.5	HE (10)	30	$Yb(OTf)_3$ (5)	0
3	1.5	HE (10)	30	$Sc(OTf)_3$ (5)	0
4	1.5	HE (10)	30	$HfCl_4$ (5)	0
5	1.5	HE (10)	30	$ZrCl_4$ (5)	0
6	1.5	HE (10)	30	$AlCl_3$ (5)	2
7	1.5	$SnCl_2$ (5)	30	/	78
8	1.5	CuCl (5)	30	/	0
9	1.5	$FeCl_2$ (5)	30	/	0
10	1.5	$SnCl_2$ (10)	30	/	73
11	1.5	$SnCl_2$ (5)	30	$SnCl_4$ (5)	73
12	1.5	$SnCl_2$ (5)	30	$FeCl_3$ (5)	69
13	1.5	$SnCl_2$ (5)	30	$AlBr_3$ (5)	80
14	**1.5**	**$SnCl_2$ (5)**	**30**	**$AlCl_3$ (5)**	**97**
15	1.0	$SnCl_2$ (5)	30	$AlCl_3$ (5)	75
16	2.0	$SnCl_2$ (5)	30	$AlCl_3$ (5)	98
17	1.5	$SnCl_2$ (5)	0	$AlCl_3$ (5)	8
18	1.5	$SnCl_2$ (5)	60	$AlCl_3$ (5)	85

[a] Conditions: **2** (0.1 mmol, 1.0 equiv) was added to a mixture of **1a** (1.5 equiv), initiator and Lewis acid in 0.5 mL DCE that was pre-stirred for 10 min, stirred for 3 h, and then quenched by MnO_2. Yields were determined by ^1H NMR using 1,1,2,2-tetrachloroethane as internal standard.

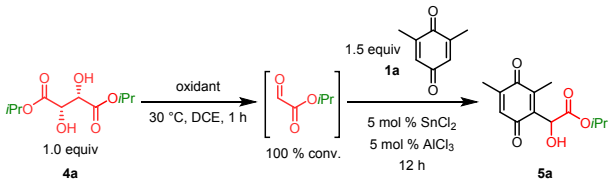
With the optimized conditions (Table 1, entry 14) in hand, the substrate scope was investigated. Broad ranges of quinones provided various QHEAs in up to 81 % isolated yields (Scheme 2). In addition to alkyl and aryl substituted (**3c**-**g**) quinones, the reaction exhibited nice tolerance for groups with various electronic effects. The quinones substituted with both electron-donating groups (**3h**-**j**) and electron-withdrawing groups (**3k**, **l**) afforded reasonable yields in this system. The naphthoquinone (**3m**) could also serve as the reactant with a high yield. For mono-substituted benzoquinones with multiple possible reactive positions, only moderate regioselectivity were achieved (**3n**-**q**), which slightly preferred the *para* position of the quinone substituent. Unfortunately, other carbonyl-containing substrates including pyruvates were unable to exhibit any reactivity (Scheme S1).

Scheme 2. Product scope for QHAEs[a]



[a] Reactions were performed on a 0.20 mmol scale in 1.0 mL DCE. Isolated yields were reported.

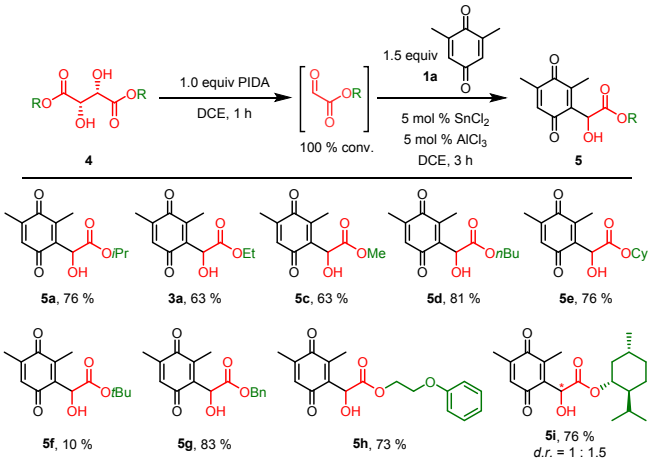
Table 2. Screening of the oxidants[a]



Entry	Oxidant	Yield (%)
1	0.5 equiv H_5IO_6	0
2	0.5 equiv $NaIO_4$	0
3	2.0 equiv quinone 1a	0
4	0.5 equiv PIDA	29
5	**1.0 equiv PIDA**	**97**
6	2.0 equiv PIDA	0
7[b]	0.50 equiv PIDA	0

[a] Unless otherwise noted, 0.1 mmol **4a** (1.0 equiv) was mixed with the oxidant in 0.5 mL DCE for 1 h, then added to a solution of 0.3 mmol **1a** (1.5 equiv), 0.01 mmol $SnCl_2$ (5 mol %) and $AlCl_3$ (5 mol %) in 0.5 mL DCE, stirred for 3 h, then quenched by MnO_2. Yields were determined by ^1H NMR using 1,1,2,2-tetrachloroethane as internal standard. PIDA = phenyliodine diacetate. [b] PIDA, **1a**, **4a**, $SnCl_2$ and $AlCl_3$ were added to 1.0 mL DCE in one portion.

Scheme 3. Product scope for tartrates[a]

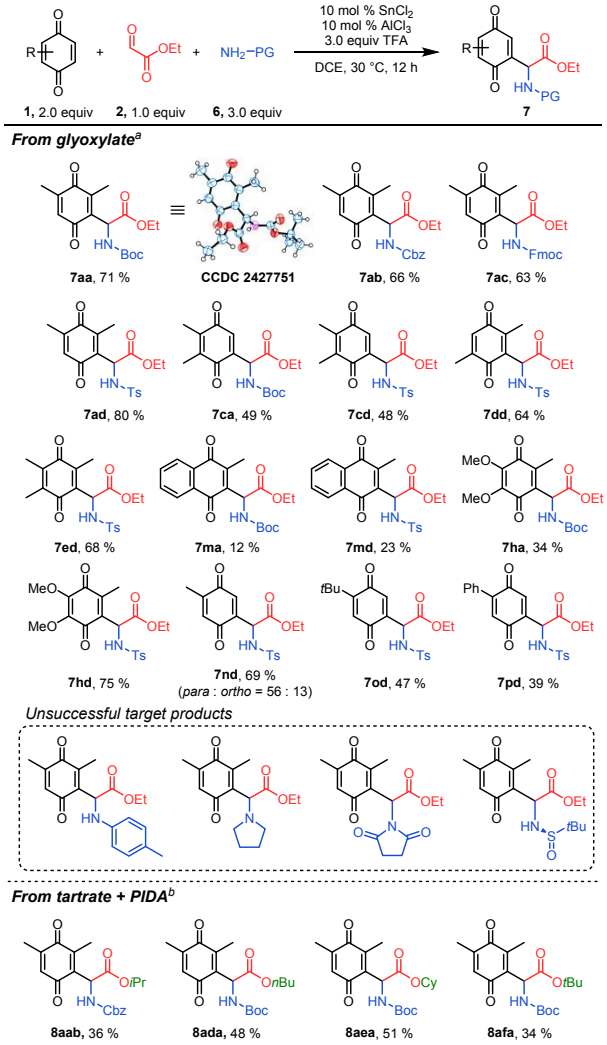


[a] Reactions were performed on a 0.2 mmol scale following standard conditions and procedures. Isolated yields were reported.

Next, glyoxylates with different ester groups were investigated as reactants. These compounds were typically synthesized through oxidation of corresponding tartrates.[32, 33] However, due to the relatively high reactivity of glyoxylates, an alternative approach was implemented in which the glyoxylates were generated by *in situ* oxidation of corresponding tartrate esters, enabling a "one-pot" reaction. Diisopropyl tartrate **4a** was used as the model reactant to study the conditions (Table 2). Inorganic oxidants such as periodic acid (H_5IO_6) and sodium periodate ($NaIO_4$) failed to afford the desired products (Table 2, Entries 1 and 2). Increasing the amount of quinone **1a**, as itself could also serve as the oxidant, did not work either (Table 2, Entry 3). On the other hand, phenyliodine diacetate (PIDA) had been disclosed as a viable oxidant for the cleavage of tartrates.[34, 35] Stoichiometry study (Table 2, Entries 4-6) found that mixing **4a** with 1.0 equiv of PIDA for 1 h, which was then subjected to react with quinone **1a** and the catalyst in the same flask, was sufficient to afford the product **5a** in the highest 97% yield. The intermediate glyoxylate was confirmed by the crude NMR spectrum. A smaller amount of PIDA could not convert all the tartrate **4a**, while a larger amount of PIDA inhibited the reaction likely by consumption of the reductive initiator in the following step. Likely for the same reason, if the tartrate and PIDA were mixed with quinone altogether instead of stepwise mixing, no product was observed (Table 2, Entry 7). Note that the stoichiometry of the reaction between tartrate and PIDA is 1:1, and 2 equiv of glyoxylate would be generated afterwards. In order to avoid ambiguity regarding stoichiometry, the amount of PIDA was calculated based on the tartrates as 1 equiv, while in the subsequent redox chain reaction, reagents including the quinone and catalysts were calculated taking the *in situ* generated glyoxylates as 1 equiv.

Investigation of the scope for esters was then possible using different tartrates as the starting materials (Scheme 3). The tartrates with primary or secondary alkyl esters (**5a-e**) furnished reasonable yields. Unfortunately, *tert*-butyl ester (**5f**) only provided a poor result, probably due to its higher reactivity of hydrolysis in the presence of Lewis acids.[36] Benzyl ester (**5g**) and ether bonds (**5h**) were both tolerated in this system. Chiral (-)-menthol ester (**5i**) afforded the product in good yield but low diastereoselectivity.

Scheme 4. Product scope for QAAEs



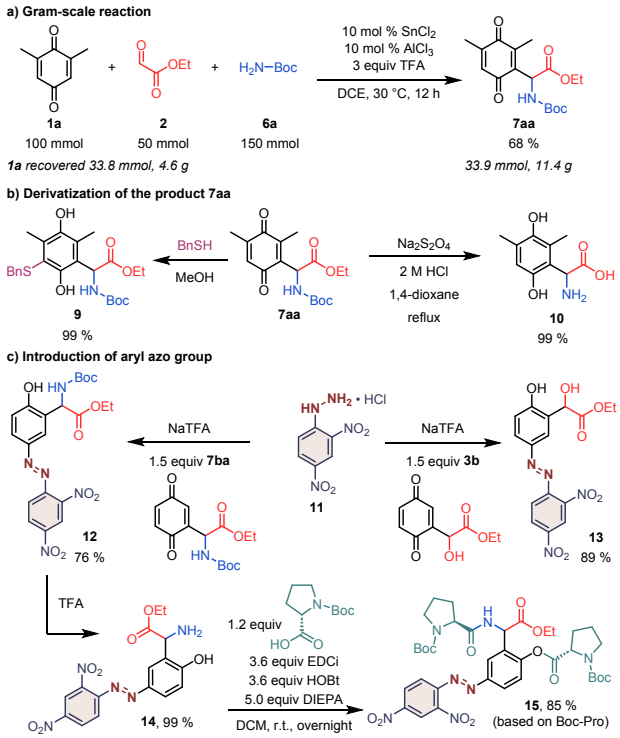
[a] To a mixture of **1** (2.0 equiv), **6** (3.0 equiv), $SnCl_2$ (0.1 equiv), $AlCl_3$ (0.1 equiv) and TFA (3.0 equiv) in 1.0 mL DCE that was pre-stirred for 10 min, **2** (0.2 mmol, 1.0 equiv) was added and stirred at 30 °C for 12 h, then quenched by MnO_2. [b] **4** (0.1 mmol, 1.0 equiv) was mixed with 1.0 equiv PIDA in 0.5 mL DCE for 1 h, then added to a solution of **1a** (1.5 equiv), **6** (3.0 equiv), $SnCl_2$ (0.1 equiv), $AlCl_3$ (0.1 equiv) and TFA (3.0 equiv) in 0.5 mL DCE, stirred for 12 h, then quenched by MnO_2. Isolated yields were reported.

The successful synthesis of QHAEs prompted us to investigate QAAEs from corresponding imines. Since many imines were challenging in isolation and purification, a three-component one-pot Mannich-type method[37] was established for *in situ* generation of imines in the presence of trifluoroacetic acid (TFA). Various QAAEs were successfully synthesized with this strategy (Scheme 3, see also Table S1 for detailed optimization of conditions). In general, the stoichiometries of **1** and **6** were increased to 2.0 equiv and 3.0 equiv respectively, so as to promote the conversion of **2** at a reasonable cost. The structure of the product was confirmed by the single crystal X-ray diffraction (scXRD) analysis of **7aa** (CCDC 2427751). Product derived from *p*-toluenesulfonamide (**6d**) led to a higher yield

than that from *tert*-butyl carbamate (**6a**). Notably, the quinones **1h** and **1m** would still favour the QHAE products instead of QAAEs. Monosubstituted quinones usually afforded only one regioisomer (**7od**, **7pd**) except **7n**. Aryl or alkyl amines[38, 39] showed no reactivity in this system, nor did the Ellman's chiral sulfinamide.[40] Moreover, this method could be combined with the oxidation of tartrates to obtain products containing different esters (**8**). Similar to the previous strategy, the tartrates were first oxidized by PIDA for 1 h to form the glyoxylates in situ, subsequently reacting with amides, quinones and catalysts to afford the QAAEs with different ester groups.

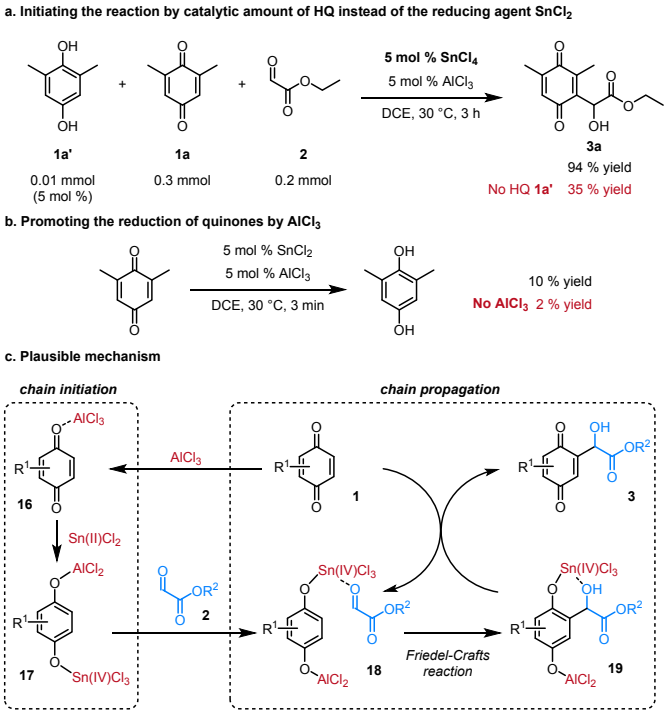
To demonstrate the practical potential of the methods, the reaction was scaled up to 50 mmol between **1a**, **2** and **6** under standard conditions, affording 11.4 g product **7aa** in 68 % yield, meanwhile recovering excessive quinone **1a** 4.6 g (Scheme 5a). The product **7aa** could be further functionalized by the addition of thiol (**9**). The quinone was reduced with sodium dithionite to prevent possible side reactions during its hydrolysis to amino acid (**10**) (Scheme 5b). Both QAAE (**12**) and QHAE (**13**) were able to react with hydrazinium chlorides to afford aryl azo products,[41] and the derivative **14** was coupled with *N*-protected proline to form a dipeptide **15** (Scheme 5c). Note that this reaction preferred double acylation at both N and O in the same molecule even at the presence of excessive **14**.

Scheme 5. Synthetic applications of QHAEs & QAAEs



Finally, the mechanism of the redox chain reaction was investigated by control experiments. The reaction was effectively initiated by a catalytic amount of hydroquinone (HQ) **1a'** along with non-reducing Lewis acid $SnCl_4$, while the efficiency was dramatically decreased without **1a'** (Scheme 6a), demonstrating that the HQ intermediate was essential in the redox chain. It was also observed that $AlCl_3$ would act as a promoter for the $SnCl_2$ reduction of quinones (Scheme 6b). A plausible mechanism was then proposed taking the hydroxyalkylation as an example (Scheme 6c). The quinone **1** would first be activated by $AlCl_3$, making it more labile towards reduction by $SnCl_2$. The hydroquinolate complex **18** would immediately react with the glyoxylates **2** through a Friedel-Crafts type reaction. Then the substituted hydroquinolate complex **19** would be oxidized to the product **3** by the remaining quinone **1**, concomitantly generating the reduced hydroquinolate complex **18** for the next cycle of the redox chain.

Scheme 6. Control experiments and proposed plausible mechanism



Conclusions

In summary, we have developed a step-economical strategy to synthesize *α*-quinonyl-*α*-hydroxy/amino acid esters through redox chain reaction, catalyzed by $SnCl_2$/$AlCl_3$. This method provided many potential precursors for functional unnatural *α*-hydroxy/amino acids.

Author contributions

The manuscript was written through the contributions of all authors. All authors have approved the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

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DOI: 10.1039/D5SC05582B

The data supporting this article have been included as part of the Supplementary Information: Materials and methods, experimental procedures, and additional characterization of synthesized compounds. Crystallographic data for compound **7aa** has been deposited at the Cambridge Crystallographic Data Centre (CCDC) database under accession number 2427751 and can be obtained from https://www.ccdc.cam.ac.uk/.

Acknowledgement

Financial support for this work was generously provided by the ShanghaiTech University start-up funding. We thank the Analytical Instrumentation Center (Grant SPST-AIC10112914), SPST, ShanghaiTech University, for providing analytical facilities and services. We thank group member Mr. Huanchao Gu for his generous assistance in scXRD characterization.

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View Article Online
DOI: 10.1039/D5SC05582B

The data supporting this article have been included as part of the Supplementary Information: Materials and methods, experimental procedures, and additional characterization of synthesized compounds. Crystallographic data for compound **7aa** has been deposited at the Cambridge Crystallographic Data Centre (CCDC) database under accession number 2427751 and can be obtained from https://www.ccdc.cam.ac.uk/.